CHEMISTRY OF ANTIBIOTIC SUBSTANCES FROM *STREPTOMYCETES*

BY

JOHN WILLIAM ROTHROCK

B.S., Pennsylvania State College, 1941

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
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Introduction

Streptamine, one of the degradation products of streptomycin, was converted by oxidative degradation to a derivative of α,γ-diamino-β-hydroxyglutaric acid (1). An attempt to synthesize this compound (2) resulted in a product of different diastereoisomeric composition from that of the degradation product. It is the purpose of this investigation to degrade the acid further in order to prove conclusively its structure.

Discussion Of Results

N,N′-Dibenzoylstreptamine (3) was oxidized to α,γ-dibenzamido-β-hydroxyglutaraldehyde by periodate. The crystalline material isolated from the reaction mixture was the hydrated, cyclic form of this dialdehyde; namely, 2,4,6-trihydroxy-3,5-dibenzamidotetrahydropyran. Oxidation of this material by chromic acid, nitric acid, hydrogen peroxide or metal oxides gave brown, non-crystallizable oils. However, α,γ-dibenzamido-β-hydroxyglutaric acid was obtained in yields up to 62 per cent by oxidizing the dialdehyde for several days at room temperature in a large volume of water almost saturated with bromine. The acid was isolated from the reaction mixture as the calcium salt. The corresponding dimethyl ester was prepared in an almost quantitative yield with diazomethane.

Dehydration studies were carried out using N-benzoyl-DL-allothreonine methyl ester and N-benzoyl-O-methyl-DL-allothreonine methyl ester as model compounds with the expectation of developing a method applicable to the dehydration of α,γ-dibenzamido-β-hydroxyglutaric acid. Attempts to replace the hydroxyl group by a halogen atom, which could be removed by reduction or dehydrohalogenation, were unsuccessful. The models were converted to the corresponding unsaturated com-

pounds by the action of sodium *t*-butoxide in anhydrous *t*-butanol or with sodium ethoxide in absolute ethanol. However, these reagents had no effect on dimethyl α,γ-dibenzamido-β-hydroxyglutarate.

α,γ-Diamino-β-hydroxyglutaric acid was not reduced by red phosphorus and hydriodic acid in a sealed tube reaction.

Treatment of dimethyl α,γ-dibenzamido-β-hydroxyglutarate with methylsulfonyl chloride resulted in two products: (a) the corresponding β-mesyl ester in a 20 per cent yield, and (b) 2-phenyl-4-carbomethoxy-5-(carbomethoxy, benzamido)-methyl-oxazoline in an 80 per cent yield. The structure assigned to the oxazoline was supported by infrared analysis. Since these two compounds were separated with difficulty and the desired product was obtained in a low yield, indirect replacement of the hydroxyl group with a halogen atom by way of the mesyl derivative was abandoned in favor of the more promising acetoxy procedure.

Dimethyl α,γ-dibenzamido-β-acetoxyglutarate was prepared by treating the corresponding β-hydroxy ester with acetic anhydride. Acetic acid was removed from this compound by heating at 170-190°. Infrared analysis indicated the pyrolysis product was unsaturated. Reduction of this material without further purification yielded a mixture of two isomeric dimethyl α,γ-dibenzamidoglutarates. These isomers were separated and found to be identical in every way with the corresponding synthetic materials.

The isomeric dimethyl and diethyl α,γ-dibenzamidoglutarates, prepared synthetically (4), were separated on the basis of their solubilities in cold acetone. These esters were converted to the corresponding isomeric acids.

The stereochemical configurations of the isomeric dimethyl α,γ-dibenzamidoglutarates were investigated by conversion to the corresponding dihydroxy acids and identification of these compounds as known dianilides and di-*p*-toluidides. A mixture of *meso* and racemic derivatives was obtained from each iso-

mer. Evidentaly, epimerization occurred in the nitrous acid reaction. Since the extent could not be estimated, this reaction was of little or no value in establishing the configuration of these isomeric esters. By a similar method the relationship of the hydroxyl and amino groups in α,γ-diamino-β-hydroxyglutaric acid was investigated. Conversion to the corresponding trihydroxyglutaric acid with nitrous acid seemed promising, since several isomers of the latter substance were known as products of the oxidation of pentoses with nitric acid. However, the deamination reaction did not proceed in the normal manner since no trihydroxyglutatic acid derivative could be obtained.

Summary

N,N′-Dibenzoylstreptamine was prepared from streptomycin. α,γ-Dibenzamido-β-hydroxyglutaraldehyde, prepared from this product, was converted in a satisfactory yield to α,γ-dibenzamido-β-hydroxyglutaric acid. The corresponding dimethyl ester was also prepared.

Treatment of dimethyl α,γ-dibenzamido-β-hydroxyglutarate with methylsulfonyl chloride yielded the corresponding β-mesyl ester and 2-phenyl-4-carbomethoxy-5-(carbomethoxy, benzamido)-methyloxazoline.

The isomeric diethyl and dimethyl α,γ-dibenzamidoglutarates were separated from a synthetic mixture, and the corresponding acids prepared.

Dimethyl α,γ-dibenzamido-β-hydroxyglutarate was converted to a mixture of isomeric dimethyl α,γ-dibenzamidoglutarates, which were found to be identical in every way with synthetic materials.

The stereochemical configurations of α,γ-diamino-β-hydroxyglutaric acid and the dimethyl α,γ-dibenzamidoglutarates could not be determined by conversion to the corresponding hydroxy deivatives with nitrous acid.

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VITA

The author was born on January 6, 1920, in Bangor, Pennsylvania, where he received elementary and high school education. He entered the Pennsylvania State College in September, 1937, and received a Bachelor of Science degree from that institution in June, 1941. The following semester he studied in the Graduate College of the University of Wisconsin as an Alumni Research Fellow. He was employed for eighteen months by the Trojan Powder Company in the production of T.N.T. In September, 1943, he joined the Army Air Force where he was trained and served as a navigator during the following two and one-half years. He entered the Graduate College of the University of Illinois in February, 1946. In the department of chemistry he held a teaching assistantship for one semester, a research fellowship for two years, and a Du Pont Fellowship for two semesters.

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